In the United States Court of Federal Claims
OFFICE OF SPECIAL MASTERS

SIDNEY BROUSSARD, Personal Representative of the Estate of DANA BROUSSARD,	*	
	*	No. 18-302V
	*	Special Master Christian J. Moran
Petitioner,	*	Filed: April 4, 2024
v.	*	
SECRETARY OF HEALTH AND HUMAN SERVICES,	*	
Respondent.	*	

Ronald Homer and Joseph Pepper, Conway Homer, P.C., for petitioner;
Mark Hellie, United States Dep't of Justice, Washington, DC, for respondent.

DECISION DENYING ENTITLEMENT TO COMPENSATION[1]

Ms. Dana Broussard alleged that the hepatitis B vaccine caused her to suffer transverse myelitis ("TM") and neuromyelitis optica ("NMO").[2] Pet., filed Feb.

[1] Because this Decision contains a reasoned explanation for the action taken in this case, it must be made publicly accessible and will be posted on the United States Court of Federal Claims' website, and/or at https://www.govinfo.gov/app/collection/uscourts/national/cofc, in accordance with the E-Government Act of 2002. 44 U.S.C. § 3501 note (2018) (Federal Management and Promotion of Electronic Government Services). This means the Decision will be available to anyone with access to the internet. In accordance with Vaccine Rule 18(b), the parties have 14 days to identify and move to redact medical or other information, the disclosure of which would constitute an unwarranted invasion of privacy. Any changes will appear in the document posted on the website.

[2] Ms. Broussard passed away during the litigation, and her husband, Mr. Sidney Broussard, is now the named petitioner in this matter.

28, 2018. The Secretary disputed this allegation, contending that Ms. Broussard failed to prove that there is a causal link between her hepatitis B vaccination and her NMO. The parties developed their positions by presenting expert reports, arguing through legal memoranda, and presenting testimony.

The evidence, viewed in its entirety, does not preponderate in favor of finding that the hepatitis B vaccine caused Ms. Broussard's NMO. The evidence is not persuasive to demonstrate that molecular mimicry is a reliable mechanism for casually connecting the hepatitis B vaccine to NMO. Accordingly, Ms. Broussard is not entitled to compensation.

I. Facts

A. Facts about Ms. Broussard

Ms. Broussard was born in October 1966. Before her vaccination, significant medical problems included hypertension, prediabetes, and high levels of LDL cholesterol. Exhibit 2.1 at 65, 70, 92-93.[3]

Ms. Broussard received three doses of the hepatitis B vaccine – the first one on October 25, 2015, the second one on November 22, 2015, and the third one on April 24, 2016. Exhibit 2.3 at 1285. After the third dose of the hepatitis B vaccine, she started to experience severe back pain, which was "like nothing [she] had ever experienced." Exhibit 19 at 1-2. She went to the emergency room on May 7, 2016 and complained of "right flank pain, started 2 days ago, comes and goes, non radiating, not better with hydrocodone and a[n] unknown muscle relaxant." Exhibit 7 at 151. She was admitted to Kaiser Permanente Panorama City Hospital on May 8, 2016. See Exhibit 2.3 at 1486.

While Ms. Broussard was at the hospital, she underwent a series of exams, including MRI scans. On May 8, 2016, a lumbar and thoracic spine MRI without contrast revealed: "Extensive white matter high signal of the spinal cord extending from the T3-4 level through the conus. Etiologies include transverse myelitis, ischemia, and multiple sclerosis. There is mild multilevel degenerative change. There is mild scoliosis." Exhibit 2.3 at 1251. The following day, she had a cervical, thoracic, and lumbar spine MRI with contrast: "The abnormality within

[3] Since there are different page numbers shown on each page of the exhibit, for the sake of consistency, this decision will cite to the page numbers that are displayed on the bottom center of each page.

the spinal cord is again noted but has extended more cephalad when compared to the [May 8, 2016] exam. Etiologies include ischemia, an aggressive demyelinating process, and infection." Id. at 1259. A brain MRI was normal. Id. at 1261-62. On May 10, 2016, her ANA was 1:640. Id. at 1011. A progress note on May 11, 2016 documented her reports of leg weakness, loss of sensation in her legs, and inability to move her legs. Id. at 1340.

Throughout her stay at the hospital, the doctors ordered MRIs to compare her conditions to the ones shown on previous MRIs. On May 15, 2016, she had a cervical and thoracic spine MRI: "Compared to [the May 9, 2016 MRI], again noted is abnormal signal in the spinal cord and it is increased as described." Id. at 1264. On the same day, she had a brain MRI which revealed "[m]ild bilateral nonspecific white matter changes." Id. at 1266. On May 22, 2016, her cervical and thoracic spine MRI revealed:

> Diffuse intraparenchymal T2 bright signal involving the mid to lower cervical spinal cord and extending to the mid thoracic spinal cord. The superior extent of abnormal signal extends to the C4-5 level. This represents an improvement since the prior exam[4] at which time it extended to the C2 level. The inferior extent appears grossly unchanged.

Id. at 1272. She continued to complain of leg weakness. Id. at 1407, 1452-53, 1462-63. Despite having completed steroids, first plasmapheresis cycle of 5 days and Rituxan, she did not have "significant improvement in her lower extremity sensation or strength (0/5)." Id. at 1487. On May 26, 2016, while she was on her second cycle of plasmapheresis (day 3 of 5), the neurology team at Panorama City Hospital transferred her to another Kaiser medical facility in Los Angeles for a second opinion and possible change in therapy. Id. at 1486-87.

Once Ms. Broussard was transferred to Kaiser Permanente Los Angeles Medical Center, she saw a neurologist, Dr. Prasanth Manthena. Dr. Manthena examined her and noted that she had "a classic presentation of NMO transverse myelitis." Exhibit 6 at 15. He also commented that it was "unclear if any active disease [was] present at this point" and that "NMO may have overlap with [systemic lupus erythematosus due to her positive ANA]." He referred her to a

[4] Presumably, this "prior exam" refers to the May 15, 2016 MRI. The "Comparison" notes on the May 22, 2016 MRI study state "No previous study available for comparison," which might have been a typographical error.

neuroimmunologist, Dr. Brandon Beaber. Dr. Beaber wrote: "[Ms. Broussard] developed cervicothoracic transverse myelitis with onset on 5/8/16 who has been found to have anti AQP4 + neuromyelitis optica. She has several other positive autoimmune serologies but [no history] of prior autoimmune disease." Exhibit 2.3 at 1507. Dr. Baeber recommended her to have a dose of IV Cytoxan, and she agreed to undergo treatment. Id. at 1508. She was discharged from Kaiser Permanente Los Angeles Medical Center on May 31, 2016. According to the discharge summary notes, Ms. Broussard had a diagnosis of NMO transverse myelitis and had "improved sensation to heat and pressure in bilateral feet after receiving [C]ytoxan." Id. at 1532.

From May 31, 2016 to June 22, 2016, Ms. Broussard remained hospitalized at the Northridge Hospital Medical Center. Exhibit 22.4 at 1929. Her admission and discharge diagnoses were "[t]ransverse myelitis, secondary to neuromyelitis optica associated with paraplegia." Id. She was then transferred to CareMeridian Texhoma House on June 22, 2016 and "discharged [at an] unknown date." Exhibit 5 at 1. She "progressed serially, did quite well, regained function and was able to be transferred to Northwest Hospital Acute rehab to continue her treatment." Id.

On July 6, 2016, Ms. Broussard had a follow-up visit with Dr. Beaber. Dr. Beaber noted that she had "only minimal improvement" and "had some temporary improvement in sensation." Exhibit 2.1 at 149. Dr. Beaber wrote that Ms. Broussard's "husband is convinced that the hepatitis B vaccine caused her condition." Id. Dr. Beaber reported that he "did in fact report a possible vaccine adverse event to the VAERS system through CDC even though there is no specific known association between vaccines and NMO." Id. at 150. On the VAERS report, Dr. Beaber wrote: "The patient received the HBV (adult) 3rd dose on 4/24/16 and developed severe cervicothoracic transverse myelitis on 5/8/16 and was subsequently diagnosed with neuromyelitis optica." Exhibit 6 at 1.

In mid-July 2016, Ms. Broussard saw a neurologist, Dr. Simon Wu. Exhibit 2.1 at 197-200. He recorded that she felt "tingling, heat sensation, ice" and "some sensation at level just above buttocks." Id. at 197. He documented her reports: "Thinks it is due to [Hepatitis] B vaccine, [p]er husband 'perfectly healthy before.'" Id. He "[d]iscussed Urodynamics study to obtain baseline evaluation of her currently lower urinary tract function."[5] Id. at 200. A few weeks later, on July 28, 2016, Ms. Broussard underwent a cervical and thoracic spine MRI. The MRI

[5] In September 2016, Ms. Broussard underwent a urodynamics study, "showing detrusor function and at least partial emptying of bladder with void." Exhibit 2.1 at 301.

findings were: "There is abnormal T2 hyperintensity within the cord which extends from C6/C7 to approximately T10. The superior extent of the signal abnormality in the cord has decreased since the [May 22, 2016] exam. Previously the cord signal abnormality began at the level of C5." Exhibit 2.1 at 245-46.

From August 2016 to December 2016, Ms. Broussard continued to seek treatment from various providers. The medical notes throughout this period generally documented some improvement in her lower extremities. See e.g., Exhibit 2.1 at 300, 421; Exhibit 5 at 17. In November 2016, she reported that she had "sensation in legs, [could] feel touch," and was "sensitive to touch and pain," but she could not "move lower extremities, remain[ed] biplegic and [was] using [a] wheelchair." Exhibit 8 at 1. She had "paresthesias, electrical sensation, [and] cramps in legs while lying down." Id. In mid-December 2016, she was admitted to the hospital for "left popliteal vein deep venous thrombosis with underlying cellulitis." Exhibit 2.2 at 811. After she was discharged, she had a follow-up appointment with a physical medicine and rehabilitation specialist, Dr. Satinderpal Dhah, who noted that she had an "improved tone" which "allowed for increased independence and ease with transfers, mobility, bladder and bowel program, hygiene . . ." Id. at 841.

In addition to seeking medical treatment from various providers, Ms. Broussard also underwent independent medical evaluations with Dr. Jacobo Chodakiewitz for her worker's compensation claim. Exhibit 64 at 232. One of the evaluations took place on November 7, 2016, and Dr. Chodakiewitz submitted a report on December 1, 2016, stating: "After reviewing the patient's medical history, medical records, and my physical examination, it is my current opinion that the issue of medical causation is related to the injury of April 24, 2016." Id.

In 2017, Ms. Broussard's conditions persisted. From March 2, 2017 to March 17, 2017, she was admitted for inpatient rehabilitation and she complained of "increasing spasticity in the lower extremities." Exhibit 13.1 at 3. "At the time of discharge, [Ms. Broussard] was independent in feeding and grooming," and she "needed minimal assist[ance] for bathing, upper body dressing, toilet transfers, tub transfers, [and] moderate assist[ance] for lower body dressing and toileting." Id. at 4. She "was at the modified independent level for wheelchair mobility" and "needed total assist[ance] for gait with a front-wheeled walker up to 75 feet. Id. At a follow-up appointment in April 2017, she reported that she continued "to have spasticity in the legs on and off . . ." and that she recently "started to have pain in both thighs . . . causing difficulty in sleeping at night." Exhibit 13.2 at 566. She continued to be wheelchair bound. See Exhibit 8 at 11, Exhibit 13 at 567.

In August 2017, Ms. Broussard went to an immunotherapy physician, Dr. Richard Burt. Exhibit 17 at 1. He observed from her neurologic examination: "She can move her arms with normal strength but can barely move her knees and straighten her legs against gravity, but no dorsiflexion of the feet. She can slightly lift her right thigh against gravity, but not the left. She cannot stand without bilateral assist[ance]. Even then she cannot hold her weight and falls down." Id. at 2. Dr. Burt's assessment noted that her complications "occurred suddenly 2 weeks after a hepatitis B vaccine and suggests this is a vaccine related sudden demyelinating event, a one time episode of which she has had [a] very incomplete recovery and probably not neuromyelitis optica." Id. He stated that her "thoracic spine has possible T2 to T10 central canal edema, again possibly suggesting a post-hepatitis B vaccine related acute demyelinating event." Id.

Five months later, in the beginning of January 2018, Ms. Broussard started another round of therapy for bilateral lower extremity weakness, impaired proprioception and lower extremity sensation, and bilateral lower extremity atrophy. Exhibit 24 at 5. She sought physical treatment twice a week for eight weeks. Id. By February 21, 2018, she reported that she was "able to move legs more . . . nearly lift both legs up against gravity." She had "[i]mproved muscle activity" and her "[left] ankle boot has been [discontinued]." Id.

Since then, Ms. Broussard continued to seek treatment for her NMO from neurology, neuroimmunology, urology, psychiatry, and physical therapy specialists. See Exhibits 24, 47-53, 56-58, 61-66, 68-69.

On June 2, 2022, the undersigned conducted a hearing to listen to testimony from Ms. Broussard's expert and respondent's expert. Ms. Broussard did not testify at the hearing. While the parties were in the process of submitting post-hearing briefs, Ms. Broussard passed away.

B. NMO

NMO is a rare autoimmune demyelinating disease in which a certain antibody attacks certain parts of the central nervous system, specifically the aquaporin-4 water channels found in the optic nerve and spinal cord, in a process known as "astrogliopathy." Exhibit 29 at 618;[6] Tr. at 21, 33, 200. The aquaporin-

[6] JL Bennett et al., Intrathecal pathogenic antiaquaporin-4 antibodies in early neuromyelitis optica, 66 Ann Neurol. 617 (2009), filed as Exhibit 29.

4 water channels are present in astrocytes. Exhibit 28 at 350;[7] Tr. at 60. The attack destroys the astrocytes, which are necessary for trophic support of the oligodendrocytes. Tr. at 201. Since there is no support for oligodendrocytes, they, too, become destroyed, leading to the loss of myelin and eventually secondary demyelination. Id. In sum, the loss of astrocytes leads to secondary demyelination. Id.

II. Procedural History

Ms. Broussard alleged that the hepatitis B vaccine caused her to suffer NMO. Pet., filed Feb. 28, 2018.[8] She filed medical records and then assessed the record as complete on June 15, 2018. The Secretary subsequently confirmed the record was complete and advised that he intended to defend this case. Resp't's Status Report, filed Nov. 14, 2018.

On March 5, 2019, the Secretary submitted his Rule 4(c) Report, recommending that compensation be denied. The Secretary asserted that Ms. Broussard did not provide an expert opinion setting forth a reliable medical theory showing that the hepatitis B vaccine caused her conditions. The Secretary also maintained that she did not present a logical sequence of cause and effect. To facilitate the process of presenting reports from experts, the undersigned proposed a set of instructions on March 15, 2019, which were then made final on April 1, 2019.

Six months later, in October 2019, Ms. Broussard filed a report from a neuroimmunologist, Dr. Salvatore Napoli, whom she had retained. Exhibit 25. Dr. Napoli generally opined that the hepatitis B vaccination caused Ms. Broussard's NMO. He maintained that "[m]olecular mimicry has been linked to the development of NMO due to the similarity in epitopes of AQP-4 water channels

[7] S. Saadoun, Intra-cerebral injection of neuromyelitis optica immunoglobulin G and human complement produces neuromyelitis optica lesions in mice, 133 Brain 349 (2010), filed as Exhibit 28.

[8] Although Ms. Broussard initially alleged that the hepatitis B vaccination caused her to suffer TM and NMO, this decision will limit its discussion to NMO only because both parties' experts agreed that NMO was presenting as longitudinal extensive TM. See Exhibit 25 at 5; Exhibit A at 4.

and antigens [in the] Hep B vaccination." Id. at 5. He relied on Noorbakhsh[9] to reach this conclusion; however, he cautioned that the article "focuses mainly on the hepatitis B vaccine causing ADEM (not NMO) but [the] authors further note that patients can develop ADEM/transverse myelitis, which is one of the clinical presentations of NMO." Id. Dr. Napoli cited various case studies "implicating hepatitis B vaccine in a reasonable timeline with the onset of autoimmune inflammatory central nervous system demyelinating illness." Id. at 7. He admitted that "[t]o [his] knowledge, there are no epidemiologic studies relating Hep B to TM/NMO [and] [l]ike all vaccine related injuries, the sample size of cases is too small to prove an epidemiological signal or risk, though it is clear that a risk though small can exist." Id.

The Secretary responded by submitting a report from a neuroimmunologist whom he had retained, Subramaniam Sriram, on March 26, 2020. Exhibit A. Dr. Sriram challenged Dr. Napoli's application of the molecular mimicry theory to Ms. Broussard's case. Dr. Sriram stated that the key studies, which Dr. Napoli cited in his report, did not "involve the development of neuromyelitis optica following hepatitis B vaccination" and other case reports were "not germane to the current situation" or had "no bearing on the [] case since [they do] not involve transverse myelitis or the relationship between aquaporin 4 antigen and development of an inflammatory myelopathy." Id. at 6, 7.

Ms. Broussard's expert, Dr. Napoli, submitted a responsive expert report, disagreeing with Dr. Sriram's stance on the irrelevance of the articles cited by Dr. Napoli in his initial report. Exhibit 54. Dr. Napoli reasoned that, because the "neuromyelitis optica spectrum disorder as well as multiple sclerosis fall within the family of demyelinating disease with molecular mimicry as a proposed hypothesis as a trigger for autoimmunity," the articles discussing an increased risk of multiple sclerosis associated with the hepatitis B vaccine can be extrapolated to Ms. Broussard's case regarding NMO. Id. at 1. Dr. Napoli emphasized that the articles demonstrate that there "is in fact the strong possibility that a molecular mimicry component could trigger, in a genetically prone individual, the demyelinating disease syndrome neuromyelitis optica." Id. at 2.

The Secretary's expert, Dr. Sriram, pointed out that Dr. Napoli's opinion was conclusory for several reasons. Exhibit C. According to Dr. Sriram, Dr.

[9] Noorbakhsh et al., Acute Disseminated Encephalomyelitis: Clinical and Pathogenesis Features, 26 Neuro Clin 759 (2008), filed as Exhibit 41.

Napoli did not cite to a Harvard School of Public Health study that he claimed was supposed to show an increased risk of complications within 3 years following hepatitis B vaccination.[10] Id. at 1. Dr. Napoli also did not cite to a single case of NMO following hepatitis B vaccination and failed "to recognize that attributing a cause of the disease to molecular mimicry between vaccine and self-antigens requires the fulfillment of defined criteria."[11] Id. at 2; Tr. at 223-24 (Dr. Sriram testifying that Mr. Broussard's articles have not even satisfied the first criterion of the Yuki[12] article for molecular mimicry because none of the cited literature identified cross-reactivity or homology between the hepatitis B vaccine and AQP4). Dr. Sriram reiterated that the hepatitis B vaccine did not result in the development of Ms. Broussard's NMO.

After the expert report phase concluded in August 2020, Ms. Broussard filed additional medical records and a brief. The Secretary submitted his brief on May 24, 2021 and Ms. Broussard filed her reply brief on June 14, 2021.

In August 2021, the parties reported that they did not wish to explore settlement and planned on continuing to litigate the case. A hearing was held on June 2, 2022. Dr. Napoli and Dr. Sriram testified in accord with their reports.[13] Ms. Broussard did not testify.

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[10] While Dr. Napoli did not cite this study in his expert report, Ms. Broussard did file the study as Exhibit 55. See Pet'r's Prehear'g Reply Br. at 9.

[11] Dr. Sriram listed the criteria: 1) Epidemiological studies should show a temporal relationship between a particular vaccine the disease in question. 2) Preclinical evidence of vaccine inducing an immune response to the target antigen in animal models. 3) An immune response either by presence of reactive T cells or antibodies to the target antigen needs to be present in individuals receiving the vaccine. 4) The development of an autoimmune model following vaccination and extremital animals should be present. Exhibit C at 2. Dr. Sriram concluded that "none of the criteria are fulfilled" in Ms. Broussard's case. Id. This list of criteria can be found in Yuki's Gangliosode Mimicy and Peripheral Nerve Disease. Exhibit C, Tab 1 at 691-92.

[12] Special masters have generally considered the Yuki factors in their decisions; however, the factors are not dispositive. See, e.g. Daily v. Sec'y of Health & Hum. Servs., No. 07-173V, 2011 WL 2174535 (Fed. Cl. May 11, 2011).

[13] Ms. Broussard's counsel, Mr. Pepper, asked Dr. Napoli many leading questions on direct examination. See, e.g., Tr. at 44, 54-55, 63-64. This presentation reduced Dr. Napoli's effectiveness. See J.C. Equipment Corp. v. England, 360 F.3d 1311, 1315 (Fed. Cir. 2004).

After the hearing, the undersigned ordered the parties to submit post-hearing briefs. In the meantime, Ms. Broussard passed away and her counsel notified the undersigned of her death in a status report. Ms. Broussard's post-hearing brief was filed on April 12, 2023. The Secretary filed his responsive post-hearing brief on June 20, 2023. Ms. Broussard was afforded an opportunity to submit a reply brief but did not do so. See Order, issued June 20, 2023. Ms. Broussard's counsel filed documentation on August 9, 2023 confirming Ms. Broussard's husband as the legal representative of her estate. The case caption was subsequently amended to reflect Mr. Sidney Broussard as the legal representative of his wife's estate.[14]

With the filing of the parties' post-hearing briefs, the case is ready for adjudication.

III. Standards for Adjudication

A petitioner is required to establish his case by a preponderance of the evidence. 42 U.S.C. § 300aa-13(1)(a). The preponderance of the evidence standard requires a "trier of fact to believe that the existence of a fact is more probable than its nonexistence before [he] may find in favor of the party who has the burden to persuade the judge of the fact's existence." Moberly v. Sec'y of Health & Hum. Servs., 592 F.3d 1315, 1322 n.2 (Fed. Cir. 2010) (citations omitted). Proof of medical certainty is not required. Bunting v. Sec'y of Health & Hum. Servs., 931 F.2d 867, 873 (Fed. Cir. 1991).

Distinguishing between "preponderant evidence" and "medical certainty" is important because a special master should not impose an evidentiary burden that is too high. Andreu v. Sec'y of Health & Hum. Servs., 569 F.3d 1367, 1379-80 (Fed. Cir. 2009) (reversing a special master's decision that petitioners were not entitled to compensation); see also Lampe v. Sec'y of Health & Hum. Servs., 219 F.3d 1357 (Fed. Cir. 2000); Hodges v. Sec'y of Health & Hum. Servs., 9 F.3d 958, 961 (Fed. Cir. 1993) (disagreeing with the dissenting judge's contention that the special master confused preponderance of the evidence with medical certainty).

When pursuing an off-Table injury, a petitioner bears a burden "to show by preponderant evidence that the vaccination brought about [the vaccinee's] injury by providing: (1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was

[14] Since Mr. Broussard is now the petitioner in this case, the following sections will reflect Mr. Broussard as the petitioner and the pronouns will be "masculine gender pronouns."

the reason for the injury; and (3) a showing of a proximate temporal relationship between vaccination and injury." Althen v. Sec'y of Health & Hum. Servs., 418 F.3d 1274, 1278 (Fed. Cir. 2005).

IV. Analysis: Althen Prong One

At the outset, there is no need to discuss Althen Prong 3 in this decision, as there is no dispute on the issue of a temporal relationship. See Resp't's Posthear'g Br. at 19. Whether to grant or deny Ms. Broussard's compensation turns on the analysis of Althen prong 1. For the reasons explained below, Ms. Broussard is not entitled to compensation.

As part of his burden to establish that the hepatitis B vaccine was the cause-in-fact of Ms. Broussard's NMO, Mr. Broussard must present "a medical theory causally connecting the vaccination and the injury." Althen, 418 F.3d at 1278. The parties have presented different forms of evidence on this topic, including (A) epidemiologic studies, (B) case reports and case series, and (C) opinions from experts regarding molecular mimicry.[15]

A. Epidemiology

While epidemiology is not required, Althen, 418 F.3d at 1279-80, epidemiology remains relevant. For a lengthy discussion of the value of epidemiologic studies in the Vaccine Program, see Tullio v. Sec'y of Health & Hum. Servs., No. 15-51V, 2019 WL 7580149, at *5-8 (Fed. Cl. Spec. Mstr. Dec. 19, 2019), mot. for rev. denied, 149 Fed. Cl. 448, 475 (2020); see also P.M. v. Sec'y of Health & Hum. Servs., No. 16-949V, 2019 WL 5608859, at *24-25 (Fed. Cl. Spec. Mstr. Sep. 24, 2019) (finding that epidemiologic studies weighed against finding the flu vaccine can worsen multiple sclerosis); King v. Sec'y of Health & Hum. Servs., No. 03-584V, 2010 WL 892296, at *74 (Fed. Cl. Mar. 12, 2010) ("special masters have routinely found that epidemiologic evidence, and/or other medical journal articles, while not *dispositive,* should be *considered* in evaluating scientific theories").

[15] Dr. Napoli testified about the concept of epitope spreading. Tr. at 51. Since Mr. Broussard did not significantly develop this theory in his reply brief, and instead blended it in with the discussion of molecular mimicry, this decision will not have a separate section on a discussion of epitope spreading. See Pet'r's Reply Br. at 10-18, passim.

Dr. Napoli acknowledged that "there are no epidemiologic studies relating Hep B to TM/NMO." Exhibit 25 at 7; Tr. at 118, 141. Since there are no epidemiological studies directly linking the hepatitis B vaccine to NMO, Dr. Napoli relied on the MS studies to reach the conclusion that a hepatitis B vaccination could cause NMO. Dr. Napoli and Dr. Sriram each cited one epidemiological study investigating an association between the hepatitis B vaccine and MS.

Dr. Napoli submitted a prospective study from Hernán[16] to demonstrate that "immunization against hepatitis B was associated with a threefold increase in the incidence of MS within the 3 years following vaccination." Exhibit 55 at 840. The authors emphasized that their study "cannot distinguish whether the hepatitis B vaccine hastens the onset of MS in persons destined to develop the disease years later, or whether it causes new cases of MS in susceptible individuals." Id. The study "may eventually contribute to a better understanding of the etiology of MS, but any decision concerning hepatitis B vaccination needs to take into account the large benefits derived from the prevention of a common and potentially lethal infection." Id.

To contest Dr. Napoli's contention that there is an increased risk of MS following a hepatitis B vaccination, Dr. Sriram submitted a German epidemiological study from Hapfelmeier[17] to show that the results of the study "do not reveal vaccination to be a risk factor for MS [and] [o]n the contrary, they consistently suggest that vaccination is associated with a lower likelihood of being diagnosed with MS within the next 5 years." Exhibit C, Tab 2 at e908.

These two studies do not focus on NMO, and therefore, bear little weight in Ms. Broussard's case.[18] Although NMO and MS overlap because they are both

[16] Miguel A. Hernán et al., Recombinant hepatitis B vaccine and the risk of multiple sclerosis, 63 Neurology 838 (2004), filed as Exhibit 55.

[17] Alexander Hapfelmeier et al., A large case-control study on vaccination as risk factor for multiple sclerosis, 93 Neurology e908 (2019), filed as Exhibit C, Tab 2.

[18] The petitioner only mentioned the Hernán study briefly, quoting "recombinant hepatitis B vaccine is associated with an increased risk of MS and challenge the idea that the relation between hepatitis B vaccination and risk of MS is well understood" in the pre-hearing reply brief. Pet'r's Prehear'g Reply Brief at 9. The petitioner did not elaborate further and instead cited the Secretary's Hapfelmeier article: "A limitation of the present study is the subjective definition of the MS cohort, potentially leading to flawed findings." Id. at 10. It appears that the petitioner cited the Secretary's article to demonstrate that the petitioner's article is "more

autoimmune disorders, they are pathologically different. Tr. at 31, 34. Therefore, these MS studies carry less evidentiary value in Ms. Broussard's case.

B. Case Reports and Case Series

Without any epidemiological evidence that directly connects the hepatitis B vaccine with Ms. Broussard's NMO, Mr. Broussard relies upon case reports about a hepatitis B vaccine preceding the onset of NMO to support the claim that a hepatitis B vaccine can cause NMO. See Pet'r's Prehear'g Br. at 50-54; Tr. at 94-120, passim. This position is flawed because case reports provide little, if any, meaningful information about causation. At best, they show temporal data but do not necessarily demonstrate that a hepatitis B vaccine can cause NMO.

Various authorities have commented on the value of case reports. To start, the Federal Judicial Center has published a series of guides designed "to assist judges . . . in reaching an informed and reasoned assessment concerning the basis of expert evidence." Jerome P. Kassirer and Gladys Kessler, Reference Manual on Scientific Evidence, Preface (3d ed. 2011) ("Reference Manual"). The guidance from the Federal Judicial Center translates to the Vaccine Program because causation for off-Table injuries in the Vaccine Program is the same as traditional causation. See Moberly, 592 F.3d at 1322-23; Shyface v. Sec'y of Health & Human Servs., 165 F.3d 1344, 1351 (Fed. Cir. 1999) ("The absence of elaboration of the law of causation in the legislative history leads us to conclude that the Vaccine Act's requirement of causation in non-Table cases was not viewed as distinct from causation in the tort law."). For examples in which appellate authorities within the Vaccine Program have cited the Reference Manual, see Germaine v. Sec'y of Health & Hum. Servs., 155 Fed. Cl. 226, 228-29 (2021), and Hart v. Sec'y of Health & Hum. Servs., 60 Fed. Cl. 598, 607 n.20 (2004).

A pertinent guide in the Reference Manual states "[a]necdotal evidence usually amounts to reports that events of one kind are followed by events of another kind. Typically, the reports are not even sufficient to show association, because there is no comparison group." David H. Kaye and David A. Freedman, Reference Manual on Scientific Evidence, Reference Guide on Statistics, at 218.

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reliable" than the Secretary's article; however, the petitioner did not thoroughly discuss why that is the case. The Secretary, on the other hand, stated that the Hernán article has "limited value" but did not analyze it meaningfully. Resp't's Prehear'g Br. at 16. The parties cited the Hernán study in their post-hearing briefs but did not thoroughly address it. Pet'r's Posthear'g Br. at 23; Resp't's Posthear'g Br. at 16. They did not address the Hapfelmeier article in their post-hearing briefs.

These authors also state "some courts have suggested that attempts to infer causation from anecdotal reports are inadmissible as unsound methodology under Daubert." Id. at 217 n. 14 (citing cases).

Within the Vaccine Program, the Federal Circuit has endorsed, albeit indirectly, a view that case reports merit little weight. In a series of five cases involving auto-immune hepatitis, the (undersigned) special master rejected case reports as evidence of causation. Porter v. Sec'y of Health & Hum. Servs., No. 99–639V, 2008 WL 4483740, at *13 (Fed. Cl. Spec. Mstr. Oct. 2, 2008). Under the caption of a different case, a judge at the Court of Federal Claims disagreed with this weighing of evidence. Rotoli v. Sec'y of Health & Hum. Servs., 89 Fed. Cl. 71, 86–87 (2009). When the Federal Circuit reviewed the special master's decision, the Federal Circuit stated that "[t]he special master found that the remaining two articles, both describing single case studies, did not contain any meaningful analysis about causation." Porter v. Sec'y of Health & Human Servs., 663 F.3d 1242, 1253 (Fed. Cir. 2012). The Federal Circuit also stated that the "decision reveals a thorough and careful evaluation of all the evidence including . . . medical literature." Id. at 1254.

Similar indirect support from the Federal Circuit is found in W.C. W.C. v. Sec'y of Health & Hum. Servs., No. 07-456V, 2011 WL 4537877, at *13 (Fed. Cl. Spec. Mstr. Feb. 22, 2011), mot. for rev. denied on this point, 100 Fed. Cl. 440, 456 (2011), aff'd, 704 F.3d 1352 (Fed. Cir. 2013). At the trial level, the (undersigned) special master declined to rely upon case reports because, among other reasons, "case reports cannot distinguish a temporal association from a causal relationship." Id. at *13. At the Federal Circuit, the appellate court focused primarily upon epidemiologic studies, which undermined the claim that the vaccine significantly aggravated the petitioner's illness. W.C. v. Sec'y of Health & Hum. Servs., 704 F.3d 1352, 1360-61 (Fed. Cir. 2013). However, at the end of its opinion, the Federal Circuit stated that it "cannot say that the special master's . . . weighing of the scientific evidence was arbitrary or capricious." Id. at 1361.

Much of the foregoing analysis regarding case reports was set forth in K.O. v. Sec'y of Health & Human Servs., No. 13-472V, 2016 WL 7634491, at *11-12 (Fed. Cl. Spec. Mstr. July 7, 2016). After K.O., the Federal Circuit has not discussed case reports in a precedential opinion, leaving Porter and W.C. as the leading, although muted, words on the subject. Consequently, judges from the Court of Federal Claims have tended to defer to the special master's assessment of case reports. See, e.g., Kelly v. Sec'y of Health & Hum. Servs., 160 Fed. Cl. 316, 319 (2022) (indicating that the special master was not arbitrary in finding that case

reports have limited or nonexistent value); Rus v. Sec'y of Health & Hum. Servs., 129 Fed. Cl. 672, 682 (2016) (noting the special master could reasonably afford little weight to the medical literature, including case reports). An exception to this trend is Patton v. Sec'y of Health & Hum. Servs., 157 Fed. Cl. 159 (2021). In Patton, the Court ruled that the special master "erred in his prong one analysis by discounting the evidentiary value of the case reports [petitioner's expert] submitted." Id. at 168. But, Patton does not discuss Porter or W.C. Instead, Patton relies upon Paluck v. Sec'y of Health & Hum. Servs., 104 Fed. Cl. 457, 475 (2012).[19]

Outside of the Vaccine Program, district courts have examined the value of case reports in the context of claims that drugs or a medical device harmed a person. Examples include: In re: Abilify (Aripriprazole) Products Liability Litigation, 299 F.Supp.3d 1291, 1309 (N.D. Fla. 2018) ("The difficulty with case reports is distinguishing between association and causation"); In re Tylenol (Acetaminophen) Marketing, Sales Practice, and Products Liability Litigation, 198 F.Supp.3d 446, 461 (E.D. Pa. 2016) ("It is true that case reports and anecdotal evidence alone may not be sufficient support for a causation opinion. . . . However, case reports considered in conjunction with other evidence may be an appropriate basis for an expert's causation opinion."); In re Mirena IUD Products Liability Litigation, 169 F.Supp.3d 396, 451 (S.D.N.Y. 2016) ("Case reports are generally disfavored by courts as evidence of causation because they merely describe 'reported phenomena without comparison to the rate at which the phenomena occur in the general population or in a defined control group; [they] do not isolate and exclude potentially alternative causes; and [they] do not investigate or explain the mechanism of causation.'") (citation omitted).

Mr. Broussard discussed case reports showing development of autoimmune inflammatory central nervous system demyelinating illnesses after vaccinations. See Pet'r's Prehear'g Br. at 50-54. As these case reports are part of the record,

[19] Paluck states "case reports 'do not purport to establish causation definitively, and this deficiency does indeed reduce their evidentiary value. Nonetheless, the fact that case reports can by their nature only present indicia of causation does not deprive them of all evidentiary weight.'" Paluck, 104 Fed. Cl. at 475, quoting Campbell v. Sec'y of Health & Hum. Servs., 97 Fed. Cl. 650, 668 (2011). The case Paluck quotes, Campbell, cites to Rotoli v. Sec'y of Health & Hum. Servs., 89 Fed. Cl. 71, 86-87 (2009). However, the value of the opinion by the Court of Federal Claims seems questionable as the Federal Circuit, as noted above, reversed the outcome in Rotoli, and reinstated the special master's decision, which gave little weight to the case reports. Porter, 663 F.3d at 1253. Paluck, which cited Rotoli, was issued before the Federal Circuit reversed Rotoli.

they must be considered. See 42 U.S.C. § 300aa–13(a)(1) (requiring a special master to evaluate the "record as a whole"). Mr. Broussard included more than ten case reports and case series, which can be organized into the following groups: (1) one report about the hepatitis B vaccine and NMO, (2) reports about the hepatitis B vaccine and other CNS demyelinating illnesses, (3) reports about vaccines other than the hepatitis B vaccine and CNS diseases, and (4) reports about vaccines in general (including HBV) and NMO.

1. Report of the hepatitis B vaccine and NMO

Heekin:[20] The case report focused on a patient who developed seronegative NMO following exposure to HBV. Exhibit 44 at 79. This patient had no relevant past medical history but developed pain with eye movements bilaterally 11 days after receiving HBV and Tdap vaccines. Id. The authors noted that "[n]umerous case reports exist that describe a temporal relationship between HBV administration and the onset of CNS demyelinating diseases, including MS, acute disseminated encephalomyelitis, optic neuritis both unilateral and bilateral, and transverse myelitis." Id. Dr. Napoli testified this study demonstrates the importance of treating a patient based on how he or she presents clinically rather than strictly relying on (false negative) test results. Tr. at 113. Dr. Sriram, however, pointed out that it was not possible to make a causal connection between HBV and the development of NMO since the patient received both HBV and Tdap vaccines. Id. at 248-49.

2. Reports about the hepatitis B vaccine and other CNS demyelinating illnesses

Tessman:[21] This news article noted Dr. Miguel Hernán's estimation of "immunization against hepatitis B was associated with a three-fold increase in the incidence of MS within the three years following vaccination." Exhibit 42 at 1. This news article also reported that "[i]n 1996, about 200 cases of MS (and other central nervous system demyelinating disorders) following hepatitis B vaccination were reported in

[20] Richard Heekin et al., Seronegative Neuromyelitis Optica Spectrum Disorder Following Exposure to Hepatitis B Vaccination, 7 Case Rep Neurol 78 (2015), filed as Exhibit 44.

[21] Renee Tessman & Natalie Conrad, Hepatitis B Vaccine May Be Associated With Increased Risk of Multiple Sclerosis, Press Room, filed as Exhibit 42.

France, prompting the French government to suspend routine immunization of pre-adolescents in schools." Id. Dr. Napoli testified that even though the study may not be able to epidemiologically prove that the hepatitis B vaccine can cause MS, there is still a "signal" that there is a connection between the vaccine and MS, forcing the French government to suspend vaccination of students. Tr. at 104. Dr. Napoli stated that the study shows that a "vaccine-induced injury can occur." Id. He opined that it was "definitely relevant to NMO" because there is myelin damage. Id.

Tourbah:[22] The study focused on 8 patients who developed CNS inflammation less than 10 weeks after receiving the hepatitis B vaccination. Exhibit 46 at 396. The researchers cautioned, though, that a "direct causal, triggering or precipitating association between hepatitis B vaccination and encephalitis cannot be demonstrated in this study." Exhibit 46 at 400. Mr. Broussard "pointed out that the aim of the study was not to determine causality but merely to report a possible signal." Pet'r's Prehear'g Br. at 52.

Dr. Napoli testified that the purpose of this article was to demonstrate that Ms. Broussard exhibited symptoms in the same time frame that is typically expected, which is any time from four days to ten weeks. Tr. at 124. According to Dr. Napoli, the results of most patients developing symptoms after the third dose of the hepatitis B vaccine were significant because Ms. Broussard also developed symptoms after the third dose of the hepatitis B vaccine. Id. at 125. Dr. Napoli was uncertain why all of the patients in the study did not develop symptoms after the first dose; he opined that a likely reason is that everyone's clinical presentation is different – perhaps the third dose was the trigger for the symptoms. Id. at 125-26.

Tartaglino:[23] The study focused on an individual who had progressive lower-extremity numbness and difficulty walking two weeks after receiving the first dose of the recombinant form of hepatitis B vaccine. Exhibit 75 at 581. After receiving the second dose of the hepatitis B vaccine, the individual's sensory disturbance ascended to the nipple level and the individual continued to have difficulty walking. Id. Mr. Broussard

[22] A. Tourbah et al., Encephalitis after Hepatitis B vaccination: recurrent disseminated encephalitis or MS?, 53 Neurology 396 (1999), filed as Exhibit 46.

[23] L.M. Tartaglino et al., MRI Imaging in a Case of Postvaccination Myelitis, 16 AJNR Am J Neuroradiol 581 (1995).

presented this article to demonstrate a "unique case report that involved rechallenge[24] with hepatitis B vaccine." Pet'r's Br. at 52.

Dr. Napoli submitted this article to show that not only did the study's individual's disease change after the first episode, but it also progressively worsened and became more extensive after the second rechallenge. Tr. at 137. Dr. Napoli testified that he does not often see a lot of rechallenge cases, so this article presented a unique case. Id.

Dr. Sriram, on the other hand, interpreted this study in a different way. He opined that the second dose of the hepatitis B vaccine did not necessarily worsen the individual's disease course. Tr. at 269. Rather, the disease "just took a long time to evolve . . . to reach the zenith of its . . . paralysis, which takes about four to six weeks." Id.

Karussis:[25] This article noted that 71 cases of CNS demyelinating diseases were reported following vaccination, 8 of which were cases reported after the participants received the hepatitis A or B vaccines. Exhibit 40 at 215. Dr. Napoli found that this article was significant because it shows that there is "plenty of support that shows that vaccine injury can occur with NMO." Tr. at 99.

Agmon-Levin:[26] The study analyzed data from PubMed, EMBASE and DynaMed, which revealed 37 cases of transverse myelitis occurring within 3 months of hepatitis B, measles-mumps-rubella, diphtheria-tetanus-pertussis vaccinations. Exhibit 32 at 1198. The authors in this study noted that the hepatitis B vaccine has been associated with many adverse events and is the second most common vaccine reported to the U.S. Vaccine Adverse Event Reporting System. Dr. Napoli testified that this information was relevant because it warns other individuals about the potential injuries that they may have after receiving the hepatitis B vaccine. Tr. at 79.

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[24] Although Mr. Broussard presented this case report as a challenge-rechallenge case, the researchers did not describe the study as such.

[25] Dimitrios Karussis & Panayiota Petrou, The spectrum of post vaccination inflammatory CNS demyelinating syndromes, 13 Autoimmunity Reviews 215 (2014), filed as Exhibit 40.

[26] Agmon- Levin et al., Transverse myelitis and vaccines: A multi analysis, 18 Lupus 1198 (2009), filed as Exhibit 32.

3. Reports about vaccines other than the hepatitis B vaccine and CNS diseases

Furukawa:[27] The authors reported on a teenage patient with NMO after receiving the Japanese encephalitis vaccine. Exhibit 38 at e26. A few days after he received the vaccine, he "felt numbness around the abdomen and bilateral legs and difficulty urinating [and] [t]hree weeks after receiving vaccination, visual disturbance developed in the left eye, following by the right eye a few days after." Id. Dr. Napoli submitted this article to show that NMO, a rare syndrome, is implicated with a vaccine injury. Tr. at 94.

Kitazawa:[28] The authors reported on an "elderly-onset NMO patient positive for the anti-AQP-4 antibody." Exhibit 39 at 103. The patient's symptoms "developed after the diagnosis of prostate adenocarcinoma and relapsed after a 23-valent pneumococcal polysaccharide vaccination." Id. Dr. Napoli presented this article as an example of how an individual can carry AQP4 antibodies for an extended period of time without the true clinical presentation. Tr. at 38. Dr. Napoli testified that this article brings forth two issues: 1) The antibody remains dormant for a period of time, so the individual can live their life with aquaporin-4 antibody without developing NMO. A trigger, such as a vaccine, would cause the antibody to become active. 2) Not every test is accurate; for instance, a test can detect the antibody to NMO, but it is not actually NMO. Tr. at 39-40.

Wingerchuk:[29] The authors examined data from 71 NMO patients, which revealed "9% of the study population reported preceding immunizations." Exhibit 36 at 1109. They described two deceased individuals who were diagnosed postmortem with subclinical optic nerve demyelination. Tr. at 89. When they were alive, however, they had no symptomatic optic neuritis. When inquired if it is common to exhibit no

[27] Y Furukawa et al., Neuromyelitis optica after Japanese encephalitis vaccination, 18 Eur J. Neurol e26 (2011), filed as Exhibit 38.

[28] Yu Kitazawa et al., Elderly-onset neuromyelitis optica which developed after the diagnosis of prostate adenocarcinoma and relapsed after a 23-valent pneumococcal polysaccharide vaccination, 51 Intern Med. 103 (2012), filed as Exhibit 39.

[29] Wingerchuk et al., The clinical course of neuromyelitis optica (Devic's syndrome), 53 Neurology 1107 (1999), filed as Exhibit 36.

symptoms or evidence of optic neuritis in NMO, Dr. Napoli responded in the affirmative. Tr. at 90.

4. Reports about vaccines in general (including HBV) and NMO

Mealy:[30] The study examined the "prevalence of MS relapses in NMO patients either on or off preventative immunotherapy." Pet'r's Prehear'g Br. at 53. The authors concluded that "[t]he evidence suggests that there may be a risk of vaccination-associated relapses among untreated neuromyelitis optica spectrum disorder patients[.]" Exhibit 74 at 78. The authors found that "[a]mong those who were on immunotherapy to prevent relapses, there was no significant association of relapse with vaccines." Id. Dr. Napoli testified that while the study did not focus on a particular vaccine, it provided "additional data or support that vaccines can be implicated in the pathogenesis of NMO spectrum disorders." Tr. at 132, 183. Dr. Napoli agreed with the researchers that it would be beneficial to treat certain patients with preventative immunotherapy before vaccinating them, reducing the risk of a neuromyelitis optica spectrum disorder (NMOSD) relapse. Exhibit 74 at 81; Tr. at 184-85. Dr. Napoli opined that the risk of vaccination-associated relapses is generally not high and preventative immunotherapy may "reduce vaccine efficacy with prevention of a very disabling relapse." Tr. at 185. Dr. Sriram, on the other hand, disagreed with Dr. Napoli and stated that preventative treatment prior to any future vaccines is an "absolutely unnecessary step" for NMOSD patients. Id. at 250.

Menge:[31] The Menge study was based on VAERS reports and eight cases, linking NMO to vaccination in general, were retrieved from the entire VAERS database in 2012. Exhibit 37 at 285. Two out of those eight cases were reported in association with hepatitis B vaccinations. Id. The study focused on only four cases of NMO occurring in temporal association with HPV vaccinations. Id. The researchers "could not confirm humoral immunologic cross-reactivity between NMO and HPV." Id. Dr. Napoli

[30] Maureen Mealy et al., Vaccines and the association with relapses in patients with neuromyelitis optica spectrum disorder. Multiple Sclerosis and related Disorders, 23 Multiple Sclerosis and Related Disorders 78 (2018), filed as Exhibit 74.

[31] Til Menge et al., Neuromyelitis optica following human papillomavirus vaccination, 79 Neurology 285 (2012), filed as Exhibit 37.

submitted this article to show another example of vaccine injury causation, specifically demonstrating that there is a "spectrum of different cases with different vaccines." Tr. at 93. Dr. Sriram emphasized that the study suggested the HPV (and not hepatitis B) vaccine may have triggered NMO. Id. at 213.

5. Assessment of Case Reports

Mr. Broussard argued that these case reports and case series "can be more useful than large epidemiological studies that are too underpowered to provide meaningful data." Pet'r's Prehear'g Br. at 49. These case reports, according to Mr. Broussard, "strongly support Dr. Napoli's opinion that the hepatitis B vaccine can cause NMO." Id. at 54. Dr. Napoli testified that case reports are especially important, in fact "110 percent" important, when assessing causation for a rare individual. Tr. at 119. For case studies that do not specifically address NMO but address autoimmune inflammatory central nervous system demyelinating illnesses after vaccinations, Dr. Napoli agreed "110 percent" that it is relevant to "use articles that are about the etiology of multiple sclerosis or the etiology of ADEM . . . [to] draw on them as analogy to how NMO might be caused." Tr. at 174. Dr. Napoli explained that NMO and MS both create "collateral damage" in the central nervous system. Tr. at 33. Regarding NMO, he testified that "[t]hough not to an extent of MS, [there] is still . . . collateral damage of axonopathy." Id. at 34. MS also involves axonopathy and cortical brain matter lesions. Id. Dr. Napoli opined that "philosophically it is the same issue" with NMO and MS. Id.

The Secretary, on the other hand, contended that Mr. Broussard's citations to the case studies have limited value. Resp't's Prehear'g Br. at 16. According to Dr. Sriram, "different demyelinating diseases have different pathogenic pathways." Id. at 15 (citing Exhibit C at 2). Dr. Sriram wrote: "To lump all vaccines as one, fails to recognize that the immunology of individual vaccines differs and the biology of the different CNS inflammatory disease syndromes." Exhibit C at 2. The Secretary explained that, for instance, "acute disseminated encephalomyelitis (ADEM) is most likely a T-cell mediated autoimmune disease directed against neural antigens, but NMO is mediated by auto antibodies directed against the AQP4 antigen." Resp't's Prehear'g Br. at 15. The Secretary pointed out that the "Karussis study reviewed 71 case studies relating vaccination to various CNS demyelinating conditions such as ADEM, encephalitis, myelitis, optic neuritis, and NMO [and] [t]here were no case reports of Hep[atitis] B vaccination and NMO." Resp't's Prehear'g Br. at 16 (citing to Exhibit 40 at 4-5).

These case reports do not meaningfully demonstrate that the hepatitis B vaccine can cause NMO. See Whitecotton v. Sec'y of Health & Human Servs., 81 F.3d 1099, 1104 (Fed. Cir. 1996) (indicating that special masters have discretion in how they weigh evidence). The undersigned acknowledges that Dr. Napoli maintained that he relied on case reports to analogize how the hepatitis B vaccine can cause NMO because NMO is a rare disease. However, the Federal Circuit has held that special masters do not need to credit evidence when it is not properly analogized. See Bazan v. Sec'y of Health & Hum. Servs., 539 F.3d 1347, 1354 (Fed. Cir. 2008).

In Bazan v. Sec'y of Health & Hum. Servs., No. 03-0620V, 2006 WL 5616947, at *8 (Fed. Cl. Spec. Mstr. Feb. 7, 2006), the special master found that the petitioner's expert "fail[ed] to adequately explain why cases involving the [peripheral nerve stimulation] . . . can be properly analogized to those involving the [central nervous system]." The special master rejected the petitioner's expert's analogy and primarily relied upon respondent's expert, Dr. Sriram's testimony that "[j]ust because you have an inciting antigen that causes peripheral nervous system demyelinating disease, that does not necessarily extend the assumption that [the inciting antigen] can also cause central nervous system demyelinating disease." Id. at 3. Dr. Sriram explained: "Although there is myelin in both the central and the peripheral nervous system, the myelin is structurally different between the two parts of the nervous system. They don't have all the same proteins. They don't have all the same type of membrane structure either." Id. The special master denied compensation, and the petitioner filed a motion for review at the Court of Federal Claims. The Court of Federal Claims reversed the special master's entitlement decision and remanded the case to the special master "for proceedings to determine whether respondent can show by a preponderance of evidence that petitioner's illness was the result of some cause other than . . . [the] vaccination." Bazan v. Sec'y of Health & Hum. Servs., 70 Fed. Cl. 687, 700 (2006). The special master subsequently found that the petitioner was entitled to compensation. Bazan v. Sec'y of Health & Hum. Servs., No. 03-0620V, 2006 WL 5616948, at *3 (Fed. Cl. Spec. Mstr. June 30, 2006). A few years later, in 2008, the Federal Circuit held that the Court of Federal Claims erred as a matter of law in reversing the special master's original entitlement decision. Bazan v. Sec'y of Health & Hum. Servs., 539 F.3d 1347 (Fed. Cir. 2008). The Federal Circuit reversed the Court of Federal Claim's judgment, holding that "Dr. Sriram's testimony bore directly on whether the medical evidence supported concluding that the *vaccine* could be the cause-in-fact, which is clearly part of the petitioner's case-in-chief" and therefore the special master's "reliance on the government's evidence was lawful" and that there was "no other error in the special master's evaluation of this evidence, the petitioner's

evidence, or in his determination that Dr. Sriram's testimony was more credible and probative than that of [the petitioner's expert]." Id. at 1354.

Similar to Bazan, in Ms. Broussard's case, Dr. Sriram explained that it would be inaccurate for Dr. Napoli to rely on other case reports to analogize how the hepatitis B vaccine can cause NMO. Specifically, Dr. Sriram stated that it would be improper to lump all vaccines as one because doing so would ignore the immunology of different vaccines and the biology of different CNS inflammatory disease syndromes. Exhibit C at 2.

Dr. Sriram distinguished the biological process of NMO from MS. Tr. at 200. He testified that NMO is developed when there is an immune attack on the astrocytes, which have a high concentration of the AQP4 receptors. Id. The attack "leave[s] the astrocytes dead, [which] are necessary for optimal [trophic] support . . . of the oligodendrocytes." Id. at 201. The oligodendrocytes then die, causing the loss of myelin and ultimately secondary demyelination. Id. MS, on the other hand, "is a disorder in which astrocytes are normal, and the disease is a disorder of oligodendrocytes and/or myelin or both." Id. at 201. MS is "an immune activation . . . in the central nervous system leading to the loss of oligodendrocytes and/or the myelin [a]nd when the myelin is destroyed . . . the naked axons transvers[e] the nervous system." Id. at 202. These "axons then die because they don't get the trophic support from the axons . . . [leading to an axonopathy]." Id. When the axons die, "the base of the body of the neurons also do not get the trophic support so the neurons die." Id. In sum, NMO involves the attack of astrocytes whereas MS does not. Dr. Napoli appears not to have disputed Dr. Sriram's testimony on the difference between NMO and MS. Tr. at 278 (Dr. Napoli testifying that he agrees with Dr. Sriram that NMO is an astrogliopathy and MS is the opposite of that). Since there are pathological differences between NMO and MS, Dr. Napoli's case reports are not persuasive in establishing a link between the Hepatitis B vaccine and NMO.

The case reports contribute little, if anything, to the causation analysis. However, this literature is not dispositive of the issue. Therefore, the theory Mr. Broussard and his expert have put forward is addressed next.

C. Theory of Molecular Mimicry

Mr. Broussard and Dr. Napoli advance the theory of molecular mimicry to explain how the hepatitis B vaccination could cause NMO. The Secretary disputes the persuasiveness of that theory.

Because special masters are often called upon to evaluate the persuasiveness of the theory of molecular mimicry, the Court of Federal Claims and the Court of Appeals for the Federal Circuit have considered molecular mimicry in their appellate role of reviewing opinions. In December 2019, the undersigned identified the leading precedents as W.C. v. Sec'y of Health & Hum. Servs., 704 F.3d 1352 (Fed. Cir. 2013), and Caves v. Sec'y . of Health & Hum. Servs., 100 Fed. Cl. 119 (2011), aff'd sub nom., 463 F. App'x 932 (Fed. Cir. 2012). Tullio v. Sec'y of Health & Hum. Servs., No. 15-51V, 2019 WL 7580149, at *12-14 (Fed. Cl. Spec. Mstr. Dec. 19, 2019), mot. for rev. denied, 149 Fed. Cl. 448 (2020). While Tullio describes those cases in more detail, their essence appears to be that although molecular mimicry is accepted in some contexts, special masters may properly require some empirical evidence to show that a particular vaccine can cause a particular disease.

In the next approximately four years, appellate authorities reviewing decisions involving molecular mimicry have generally endorsed the approach of looking for some evidence that persuasively shows that a portion of a vaccine resembles a portion of human tissue, which contributes to causing the disease, and that the immune system will respond to the relevant amino acid sequence.[32] Chronologically, the list of more recent appellate cases begins with the opinion in Tullio, which denied the motion for review. 149 Fed. Cl. 448, 467-68 (2020).

Another example in which the Court of Federal Claims held that the special master did not elevate the petitioner's burden of proof in the context of evaluating the theory of molecular mimicry is Morgan v. Sec'y of Health & Hum. Servs., 148 Fed. Cl. 454, 476-77 (2020), aff'd in non-precedential opinion, 850 F. App'x 775 (Fed. Cir. 2021). In Morgan, the Chief Special Master found that petitioner had not presented persuasive evidence about a relevant antibody. Id. at 477. The Chief Special Master also noted that the articles about the relevant disease do not list the wild flu virus as potentially causing the disease. Id. When examining this analysis, the Court of Federal Claims concluded: "the Chief Special Master did not raise the burden of causation in this case; petitioner simply failed to meet it." Id.

[32] The term "homology" is used when discussing molecular mimicry. "Homology" is defined as "the quality of being homologous; the morphological identity of corresponding parts; structural similarity due to descent from a common form." *Dorland's* at 868.

The Federal Circuit also evaluated the Chief Special Master's approach in Morgan. The Federal Circuit concluded: "We discern no error in the special master's causation analysis." 850 F. App'x 775, 784 (Fed. Cir. 2021).

Most other recent appellate cases follow this path. See, e.g., Duncan v. Sec'y of Health & Hum. Servs., 153 Fed. Cl. 642, 661 (2021) (finding the special master did not err in rejecting a bare assertion of molecular mimicry); Caredio v. Sec'y of Health & Hum. Servs., No. 17-79V, 2021 WL 6058835, at *11 (Fed. Cl. Dec. 3, 2021) (indicating that a special master did not err in requiring more than homology and citing Tullio); Yalacki v. Sec'y of Health & Hum. Servs., 146 Fed. Cl. 80, 91-92 (2019) (ruling that special master did not err in looking for reliable evidence to support molecular mimicry as a theory); but see Patton v. Sec'y of Health & Hum. Servs., 157 Fed. Cl. 159, 169 (2021) (finding that a special master erred in requiring petitioner submit a study to establish medical theory causally connecting flu vaccine to brachial neuritis).

The Court of Federal Claims explained why petitioners must present some evidence to show the persuasiveness of molecular mimicry as a theory in their cases. Dennington v. Sec'y of Health & Hum. Servs., 167 Fed. Cl. 640 (2023), appeal dismissed, No. 2024-1214 (Fed. Cir. Mar. 25, 2024). There, Ms. Dennington alleged that a tetanus-diphtheria-acellular pertussis ("Tdap") vaccine caused her to develop GBS. Id. at 644. She supported her claim with two reports from a neurologist, Carlo Tornatore, who put forward molecular mimicry. Id. at 647-49. The chief special master denied entitlement. Id. at 656.

The Court of Federal Claims denied a motion for review because the chief special master did not commit any error in evaluating Ms. Dennington's prong one evidence. The Court emphasized the lack of evidence supporting Dr. Tornatore's opinion:

- "While Petitioner and Dr. Tornatore put forth the well-established medical theory of molecular mimicry as the mechanism through which the Tdap vaccine could cause GBS, nowhere in Dr. Tornatore's expert reports, nor in Petitioner's briefs, do they specifically tie the Tdap vaccine to GBS through molecular mimicry." Id. at 653.

- "Dr. Tornatore never actually explains how molecular mimicry might occur from the Tdap vaccine specifically, nor does he elaborate on how molecular mimicry could cause the specific autoimmune system reaction that could cause GBS." Id.

- "There is nothing in Dr. Tornatore's report that explains or even alludes to what antigens or structures in the Tdap vaccine could share homology with possible host antigens and how these antigens could react in the manner GBS is believed to progress." Id. at 654.

Based upon these observations, the Court criticized the lack of specificity in Dr. Tornatore's opinions:

> In fact, because Dr. Tornatore does not offer any specific explanation as to the distinct connection between Tdap, molecular mimicry, and GBS, one could take Dr. Tornatore's causation theory and substitute any table vaccine (e.g., the measles vaccine) and any autoimmune disorder (e.g., autoimmune encephalitis) and Dr. Tornatore's expert report's discussion of molecular mimicry would require absolutely no changes. That is how general his molecular mimicry theory is—it does not matter which vaccine and which autoimmune disorder are plugged in. But *Althen* prong one requires more.

Id.

In accordance with precedents such as W.C., Caves, Tulio, Yalacki, and Dennington, the undersigned will look to see whether any evidence supports the theory that the hepatitis B vaccine can cause NMO.

Based upon this method of analysis, the evidence Mr. Broussard presented falls short of his burden. In support of his claim that the hepatitis B vaccine caused Ms. Broussard's NMO via molecular mimicry, Mr. Broussard presented two reports and testimony from Dr. Napoli.

Mr. Broussard asserted that "molecular mimicry" is a "well-accepted biologically plausible mechanism to explain how infection and vaccination can cause CNS demyelinating disease, including NMO." Pet'r's Br. at 41. Dr. Napoli wrote:

> Vaccinations are composed of organic compounds of viral or bacterial origin. These are meant to stimulate an immune response when injected. If the antigen present on the vaccine shares any homologies

> with host antigen, then immune response will be directed at both the injected antigens and host antigen leading to an autoimmune response. This is known as molecular mimicry which is a well known response in immunology . . . AQP-4 has been identified as the protein present in astrocytes which is the target for specific NMO antibodies. Molecular mimicry has been linked to the development of NMO due to the similarity in epitopes of AQP-4 water channels and antigens Hep B vaccination. In Noorbakhsh et al, researchers found homology between myelin basic protein and the Hep B vaccine.

Exhibit 25 at 5. Mr. Broussard relied on some articles to demonstrate how the theory of molecular mimicry is applied in cases involving CNS demyelinating disorders. See, generally, Noorbaksh (Exhibit 41), Wucherphennig[33] (Exhibit 31), Fujinami (Exhibit 73).[34]

Mr. Broussard particularly focused on the Liu[35] study because it "directly implicate[s] molecular mimicry in the development of NMOSD in patients with chronic hepatitis B infection . . . . [and] provides strong support for Dr. Napoli's theory that the hepatitis B vaccine can cause NMO via the mechanism of molecular mimicry." Pet'r's Prehear'g Br. at 46. Liu et al. discussed the role of molecular mimicry in the development of NMOSD in patients with chronic hepatitis B infection:

> HBV vaccination and infection have been associated with immunological and neurological disorders such as MS, encephalomyelitis and [optic neuritis]. Although the exact pathophysiological mechanisms remain unknown, it was proposed that molecular mimicry and immunological cross-reactivity between HBsAg and myelin antigens lead to the development of demyelinating

[33] KW Wucherphennig & JL Strominger, Molecular Mimicry in T Cell-Mediated Autoimmunity Viral Peptides Activate Human T Cell Clones Specific for Myelin Basic Protein, 80 Cell 695 (1995), filed as Exhibit 31).

[34] Fujinami & Oldstone, Amino Acid Homology Between the Encephalitogenic Site of Myelin Basic Protein and Virus: Mechanisms for Autoimmunity, 230 Science 1043 (1985), filed as Exhibit 73.

[35] J. Liu et al., Comprehensive analysis of patients with NMOSD combined with chronic hepatitis B infection and seropositive antiaquaporin 4 antibody, 18 Bosn. J. Basic Med Sci 35 (2018), filed as Exhibit 43.

> diseases in the [central nervous system] and [peripheral nervous system] . . . HBsAg share high sequence homology with myelin basic protein (MBP) and myelin oligodendrocyte glycoprotein (MOG), where the viral/protein mimicking sequences may become targets of antibody response, and consequently induce the degradation of the myelin sheath as well as lead to further neurodegeneration.

Exhibit 43 at 39.

Relying on these articles, Mr. Broussard stated that they "strongly support[] that hepatitis B vaccination can cause NMO via the mechanism of molecular mimicry." Pet'r's Br. at 41. Since the medical literature for NMO may be "scant," Mr. Broussard argued that it is "imperative" to evaluate evidence in this case "generally," considering that CNS demyelinating diseases include NMO, TM, ADEM, and MS. Id. Dr. Napoli asserted that there is a shared homology between the aquaporin-4 and hepatitis B vaccine; however, there is no persuasive evidence proving as such. See Tr. at 54 (Dr. Napoli testifying that a vaccine contains a protein, and when administered to the appropriate patient, it is homologous to a similar protein on the aquaporin-4 channel), 108 (Dr. Napoli testifying that hepatitis B surface antigen does share a high sequence homology with other proteins in the central nervous system). If the special master finds that the expert's theory is supported by only an "ipse dixit," then the special master may reject this opinion. Snyder v. Sec'y of Health & Hum. Servs., 88 Fed. Cl. 706, 745 n.66 (2009).

The Secretary's expert, Dr. Sriram, however, explained that "[Mr. Broussard's] comparisons are not appropriate" because "vaccines are different from one another, derived from different sources and are either live or attenuated or represent recombinant proteins of the pathogens." Resp't's Prehear'g Br. at 14 (citing Exhibit C at 1). Dr. Sriram also pointed out that each demyelinating disease is different and, for many, the cause is not known. Id. Dr. Sriram testified that the "majority of NMO [cases]" are "idiopathic in nature" and medical experts do not know "the etiology that sets the motion out for developing an antibody response [and] sets up additional features that the antibody goes to the central nervous system and causes the astrocytes to die." Tr. at 209. Dr. Sriram further elaborated that experts do not "know all the secondary features to it [and] all [they] know is [that there] is one chemical, this antibody." Id. Dr. Sriram stated that, to his knowledge, there were no articles that "specifically look at cross-reactivity or shared homologies between the aquaporin-4 and hepatitis B." Id. at 213. He testified that none of the published studies "persuade" him to reasonably conclude

that there is a possible or potential association between hepatitis B vaccination and NMO. Id. at 209.

The Secretary, in his post-hearing brief, disagreed with Dr. Napoli's reliance on three papers, namely Heekin, Mealy, and Menge, that specifically reference the hepatitis B vaccine and NMO because none of them identify any homologous proteins. Resp't's Posthear'g Br. at 11-14. "[A]lthough Menge did examine possible homologies between HPV vaccine proteins and AQP4 through [Basic Local Alignment Search Tool] searches, the researchers 'could not confirm humoral immunologic cross-reactivity between NMO and HPV, despite theoretically shared T-cell epitopes.'" Id. (citing Exhibit 37 at 285-86).

Mr. Broussard has presented little, if any, persuasive evidence to demonstrate that molecular mimicry is a reliable basis for causally connecting the hepatitis B vaccine to NMO. At a fundamental level, Dr. Napoli did not identify any homology between the aquaporin-4 and hepatitis B vaccine. Tr. at 213. Without this basic step, Ms. Broussard's case is on par with Caves and Duncan in which appellate judges ruled that the special master did not err in declining to credit molecular mimicry. In Caves, "[w]hile the special master acknowledged that [] [petitioner's]submitted articles supported the general theory of molecular mimicry . . . he [] held that the articles do not provide any support for the more specific theory that the influenza vaccine can serve as the antigenic trigger that sets that autoimmune process into motion." 100 Fed. Cl. at 129. Furthermore, in Duncan, while "[t]he Special Master acknowledged that medical literature submitted by [petitioner] indicated that strep infections can lead to PANDAS through the process of molecular mimicry, [] [petitioner]'s experts did not identify any link between the molecular structures of strep bacteria and the HPV vaccine." 153 Fed. Cl. at 653.

Mr. Broussard has not presented preponderant evidence of a medical theory causally connecting her Hepatitis B vaccination to her NMO. Because Mr. Broussard's case is resolved based upon the first Althen prong, further evaluation of the remaining prongs is not necessary. When special masters can resolve a case a based upon one issue, they do not necessarily need to address all issues. See, e.g., Hibbard v. Sec'y of Health & Hum. Servs., 698 F.3d 1355, 1365 (Fed. Cir. 2012); Holmes v. Sec'y of Health & Hum. Servs., 115 Fed. Cl. 469, 488 (2014); Vaughan v. Sec'y of Health & Hum. Servs., 107 Fed. Cl. 212, 222 (2012).

V. Conclusion

Mr. Broussard warrants sympathy for watching Ms. Broussard suffer from her NMO. However, the requirements of the Vaccine Act must be satisfied before compensation can be awarded. Here, Mr. Broussard has not presented sufficient evidence to show that the flu vaccine caused Ms. Broussard's NMO. Accordingly, his claim for compensation is DENIED.

The Clerk's Office is instructed to enter judgment in accord with this decision unless a motion for review is filed. Information about filing a motion for review, including the deadline, can be found in the Vaccine Rules, which are available on the website for the Court of Federal Claims.

IT IS SO ORDERED.

s/Christian J. Moran
Christian J. Moran
Special Master